Title: Orthopedic Applications of Platelet-Rich Plasma

Description/Background

A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factors, epidermal growth factor, fibroblast growth factors, transforming growth factors, and insulin-like growth factors. Autologous platelets are a rich source of platelet-derived growth factor, transforming growth factors that function as a mitogen for fibroblasts, smooth muscle cells, osteoblasts, and vascular endothelial growth factors. Recombinant platelet-derived growth factor, has also been extensively investigated for clinical use in wound healing (see policy: “Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Non-Orthopedic Conditions”).

Autologous platelet concentrate suspended in plasma, also known as platelet-rich plasma (PRP), can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets, releasing the various growth factors. The polymerization of fibrin from fibrinogen creates a platelet gel, which can then be used as an adjunct to surgery with the intent of promoting hemostasis and accelerating healing. In the operating room setting, PRP has been investigated as an adjunct to various periodontal, reconstructive, and orthopedic procedures. For example, bone morphogenetic proteins are a type of transforming growth factors, and thus PRP has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries. Alternatively, PRP may be injected directly into various tissues. PRP injections have been proposed as a primary treatment of miscellaneous conditions, such as epicondylitis, plantar fasciitis, and Dupuytren contracture.

Injection of PRP for tendon and ligament pain is theoretically related to prolotherapy (see policy: “Prolotherapy”). However, prolotherapy differs in that it involves injection of chemical irritants intended to stimulate inflammatory responses and induce release of endogenous growth factors.
PRP is distinguished from fibrin glues or sealants, which have been used as a surgical adjunct to promote local hemostasis at incision sites. Fibrin glue is created from platelet-poor plasma and consists primarily of fibrinogen. Commercial fibrin glues are created from pooled homologous human donors; Tisseel® (Baxter) and Hemaseel® (Haemacure Corp) are examples of commercially available fibrin sealants. Autologous fibrin sealants can be created from platelet-poor plasma. This evidence review does not address the use of fibrin sealants.

**Regulatory Status**

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Blood products such as platelet-rich plasma (PRP) are included in these regulations. Under these regulations, certain products including blood products such as PRP are exempt and therefore do not follow the traditional FDA regulatory pathway. To date, the FDA has not attempted to regulate activated PRP.

A number of PRP preparation systems are available, many of which were cleared for marketing by FDA through the 510(k) process for producing platelet-rich preparations intended to be mixed with bone graft materials to enhance the bone grafting properties in orthopedic practices. The use of platelet-rich plasma outside of this setting (eg, an office injection) would be considered off-label. The Aurix System™ (previously called AutoloGel™; Cytomedix) and SafeBlood® (SafeBlood Technologies) are 2 related but distinct autologous blood-derived preparations that can be used at the bedside for immediate application. Both AutoloGel™ and SafeBlood® have been specifically marketed for wound healing. Other devices may be used during surgery (eg, Medtronic Electromedics, Elmd-500 Autotransfusion system, the Plasma Saver device, the SmartPReP [Harvest Technologies] device). The Magellan™ Autologous Platelet Separator System (Medtronic Sofamor Danek) includes a disposable kit for use with the Magellan™ Autologous Platelet Separator portable tabletop centrifuge. GPS®II (BioMet Biologics), a gravitational platelet separation system, was cleared for marketing by the FDA through the 510(k) process for use as disposable separation tube for centrifugation and a dual cannula tip to mix the platelets and thrombin at the surgical site. Filtration or plasmapheresis may also be used to produce platelet-rich concentrates. The use of different devices and procedures can lead to variable concentrations of active platelets and associated proteins, increasing variability between studies of clinical efficacy.

**Medical Policy Statement**

Use of platelet-rich plasma is considered experimental/investigational for all orthopedic indications. It has not been scientifically demonstrated to improve patient clinical outcomes.
Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Exclusions

Use of platelet-rich plasma is considered experimental/investigational for all orthopedic indications. This includes, but is not limited to, use in the following situations:

Primary use (injection) for the following conditions:
- Achilles tendinopathy
- Lateral epicondylitis
- Osteochondral lesions
- Osteoarthritis
- Plantar fasciitis

Adjunctive use in the following surgical procedures:
- ACL reconstruction
- Hip fracture
- Long-bone nonunion
- Patellar tendon repair
- Rotator cuff repair
- Spinal fusion
- Subacromial decompression surgery
- Total knee arthroplasty

CPT/HCPCS Level II Codes (Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)

Established codes:
N/A

Other codes (investigational, not medically necessary, etc.):
0232T  C1734

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.
To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The best evidence on the efficacy of platelet-rich plasma (PRP) consists of several RCTs comparing PRP with conservative therapy (eg, rest, physical therapy) and medication (eg. corticosteroid injection), and systematic reviews of these trials. A number of systematic reviews of RCTs, with or without the addition of observational studies on PRP, have been published; we focus on them in this evidence review. Individual RCTs are reviewed if no systematic reviews are available or if an individual RCT is likely to influence this evidence review but was not included in a systematic review.

At present, there are a large number of techniques available for the preparation of platelet-rich plasma or platelet-rich plasma gel. The amount and mixture of growth factors produced by different cell-separating systems vary, and it is also uncertain whether platelet activation before the injection is necessary.(1-6)

PLATELET-RICH PLASMA AS A PRIMARY TREATMENT FOR TENDINOPATHY

Clinical Context and Therapy Purpose
The purpose of PRP injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, and anti-inflammatory agents in patients with tendinopathy.

The question addressed in this evidence review is: does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest are individuals with tendinopathy. Patients with tendinopathy are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

Interventions
The therapy being considered is PRP injections. The use of PRP has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.
Comparators
Comparators of interest include nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, and anti-inflammatory agents. These treatments are managed by primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life (QOL), and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for tendinopathy has varying lengths of follow-up, ranging from six months to two years. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

d. Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE
Several systematic reviews have evaluated PRP for treating mixed tendinopathies. They include trials on tendinopathies of the Achilles, rotator cuff, patella, and/or lateral epicondyle (tennis elbow).

Johal et al (2019) conducted a systematic review and meta-analysis of RCTs on platelet-rich plasma for various orthopedic indications, including 10 RCTs of lateral epicondylitis.(7) The meta-analysis evaluated the standardized mean difference in pain at both 3 and 12 months. Systematic review authors used the Cochrane Collaboration risk of bias tool to assess study quality. At 12 months, pain scores were statistically significantly lower for platelet-rich plasma versus its comparators (i.e., steroids, whole blood, dry needling, local anesthetics). However, these results should be interpreted with caution due to important limitations including high statistical heterogeneity (I²=73%), lack of a clinically significant difference (i.e., < effect size threshold of 0.5 for a clinically important difference), and moderate to high risk of bias in study conduct.

Miller et al (2017) conducted a systematic review and meta-analysis on PRP for symptomatic tendinopathy and included only RCTs with injection controls.(8) The literature search, conducted through November 2016, identified 16 RCTs, with 18 groups (some studies included >1 tendinopathy site) for inclusion (N=1018 patients). The Cochrane Collaboration tool was used to assess the risk of bias: 5 studies had an uncertain risk of bias, and 11 studies had a high risk of bias. The median sample size was 35 patients. Tendinopathy sites were lateral epicondylar (12 groups), rotator cuff (3 groups), Achilles (2 groups), and patellar (1 group). Preparation of PRP differed across trials as did the number of injections, with most studies administering 1 injection and a few administering 2 injections. Eight of the 18 groups reported statistically significant lower pain scores using PRP compared with control and the
other ten reported no differences in pain scores between trial arms. A meta-analysis reported a standard mean difference (SMD) in pain scores favoring PRP over control (0.47; 95% confidence interval [CI], 0.21 to 0.72; $I^2$=67%).

Tsikopoulos et al (2016) published a meta-analysis of RCTs that compared PRP with placebo or dry needling in patients with tendinopathy lasting at least 6 weeks. (9) Minimum length of follow-up was 6 months. The primary outcome was pain intensity; the secondary outcome was functional disability. Five RCTs met reviewers’ eligibility criteria. Two RCTs addressed lateral epicondylitis, 2 rotator cuff tendinopathy, and 2 patellar tendinopathy. Three RCT studies had a saline control group, and 2 compared PRP with dry needling. In a pooled analysis of all 5 RCTs, there was no statistically significant difference in pain intensity at 2 to 3 months between PRP and placebo/dry needling (standard mean difference = -0.29; 95% CI, -0.60 to 0.02). The between-group difference in pain intensity was statistically significant at 6 months in a pooled analysis of 4 trials (standard mean difference = -0.48; 95% CI, -0.86 to -0.10). While statistically significant, reviewers noted that the difference between groups in pain intensity at 6 months was not clinically significant. Three trials reported on functional disability levels at 3 months, and meta-analysis of these trials found a significantly greater improvement in functional disability in the PRP group (standard mean difference = -0.47; 95% CI, -0.85 to -0.09). Functional disability 6 months postintervention was not addressed.

A systematic review by Balasubramaniam et al (2015) included RCTs on PRP for tendinopathy. (10) Unlike the Tsikopoulos et al (2016) review, these reviewers did not limit inclusion criteria by type of control intervention or post-intervention length of follow-up. They included 4 of the 5 RCTs in the Tsikopoulos et al (2016) review and 5 other RCTs. Four RCTs evaluated epicondylitis, 2 rotator cuff tendinopathy, 2 patellar tendinopathy, and 1 Achilles tendinopathy. Comparison interventions included placebo (n=3), dry needling (n=2), autologous blood (n=2), extracorporeal shock wave therapy (n=1), and corticosteroid injections (n=2). One study included both placebo and corticosteroid control groups. Reviewers did not pool study findings due to a high level of heterogeneity among studies. In their qualitative analysis of the literature by anatomic site of tendinopathy, they concluded that 1 trial on PRP for Achilles tendinopathy was insufficient to draw conclusions about efficacy. Findings of trials of other anatomic sites were mixed. Some showed statistically significant greater benefits of PRP than controls on outcomes, and some did not, or some found statistically significant better outcomes at some time points but not others.

Andia et al (2014) published a systematic review of PRP in the treatment of painful tendinopathies. (11) They included 13 prospective controlled trials (12 RCTs, 1 controlled trial that was not randomized) with data from 636 patients included in the meta-analysis. The trials assessed various tendinopathies, including 7 on chronic elbow, 2 on rotator cuff, 3 on patellar, and 1 study on Achilles. Control interventions included physical therapy (1 trial), extracorporeal shock wave therapy (1 trial), corticosteroid (3 trials), autologous blood (3 trials), saline (3 trials), and dry needling (2 trials). Risk of bias was considered to be low in 4 studies, unclear in 3, and high in 6. The meta-analysis found that PRP was no better than control interventions in reducing pain at 1 or 2 month follow-up. A small significant effect in pain reduction was found at 3 months (weighted mean difference, -0.61). At 1 year, the weighted mean difference between PRP and control interventions was significant at -1.56. Due to heterogeneity between studies, these findings had low power and precision.
Table 1. Systematic Reviews & Meta-Analysis Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller (2017)</td>
<td>2006-2015</td>
<td>16</td>
<td>Patients with symptomatic tendinopathy</td>
<td>median 35 (NR)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Tsikopoulos (2016)</td>
<td>2013-2014</td>
<td>5</td>
<td>Patients with tendinopathy</td>
<td>170 (23-40)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Andia (2014)</td>
<td>2010-2014</td>
<td>13</td>
<td>Patients with tendinopathy</td>
<td>636</td>
<td>Prospective</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: not reported; RCT: randomized controlled trial.

Table 2. Systematic Reviews & Meta-Analysis Results

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD in Pain for PRP</th>
<th>SMD in functional disability for PRP</th>
<th>WMD in Pain Reduction at 3 Months</th>
<th>Year (WMD between PRP and Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johal (2019)</td>
<td>-0.69</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller (2017)</td>
<td>-1.15 to -0.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsikopoulos (2016)</td>
<td>0.47</td>
<td>0.48</td>
<td>-0.86 to -0.1</td>
<td>-0.85 to -0.09</td>
</tr>
<tr>
<td>Andia (2014)</td>
<td>-0.61</td>
<td>-0.97 to -0.25</td>
<td>-2.29 to -0.83</td>
<td></td>
</tr>
</tbody>
</table>

SMD: standard mean difference; WMD: weighted mean difference; CI: confidence interval; PRP: platelet-rich plasma.

Four small RCTs (N=297, range of 57 to 80) have been published subsequent to the above-described systematic reviews. (12,13,14,15) Tendinopathy sites were lateral epicondylar (2 RCT’s), patellar (1 RCT), and gluteal (1 RCT). Follow-up durations ranged from 6 months to 1 year. Platelet-rich plasma protocols varied across studies including a single 3mL injection using a peppering technique, or ultrasound guided injections ranging from 3.5 mL to 6-7 mL. Concurrent rehabilitation protocols also differed, ranging from 6 weeks of supervised rehabilitation to 12 weeks of unsupervised rehabilitation. Compared to a corticosteroid injection, 2 RCTs found platelet-rich plasma injection to result in significantly improved pain scores. However, important relevancy gaps and study conduct limitations exist that preclude reaching strong conclusions based on this evidence. Additionally, compared to placebo, platelet-rich plasma did not significantly improve pain after 12 months. Finally, in the RCT by Martin et al (2019), compared with lidocaine, in individuals receiving platelet-rich plasma as an adjunct to ultrasound-guided tenotomy for recalcitrant elbow tendinopathy there were no significant differences in the primary outcome of rate of patients with an improvement exceeding 25% in disability based on Disabilities of the Arm, Shoulder and Hand scores (DASH-E, Spanish version), or other pain outcomes.
Table 3. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta (2019)</td>
<td>India</td>
<td>1</td>
<td>2016-2017</td>
<td>Lateral epicondylitis</td>
<td>PRP (N=40)</td>
<td>CS (N=40)</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; PRP: platelet-rich plasma; CS: corticosteroids; LR: leukocyte-rich; LP: leukocyte-poor; NR: Not reported; US: United States

Table 4. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>VAS Score</th>
<th>WOMAC</th>
<th>Other pain / disability assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin (2019)</td>
<td></td>
<td></td>
<td>1 y rate of patients with an improvement ≥ 25% in disability based on DASH-E scores</td>
</tr>
<tr>
<td>PRP</td>
<td></td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td></td>
<td>70.83%</td>
<td></td>
</tr>
<tr>
<td>Unadjusted odds ratio; 95% CI</td>
<td></td>
<td>0.71 95% CI, 0.13 to 3.84</td>
<td></td>
</tr>
<tr>
<td>Gupta (2019)</td>
<td></td>
<td>12 mo mean score</td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td>2.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>13.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.024</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scott (2019)</td>
<td></td>
<td></td>
<td>1 y NPRS</td>
</tr>
<tr>
<td>LR-PRP</td>
<td></td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>LP-PRP</td>
<td></td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td></td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick (2019)</td>
<td></td>
<td>24 wk mHHS</td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td></td>
<td>77.60</td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td></td>
<td>65.72</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>0.0003</td>
<td></td>
</tr>
</tbody>
</table>
RCT: randomized controlled trial; CI: confidence interval PRP: platelet-rich plasma; CS: corticosteroids; LR: leukocyte-rich; LP: leukocyte-poor; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; PRP: platelet-rich plasma; HA: hyaluronic acid; VAS: visual analog scale; NS: not significant; NR: not reported; NPRS: Numeric Pain Rating Scale; mHHS: Modified Harris Hip Score; DASH-E: Spanish version of the Disabilities of the Arm, Shoulder and Hand questionnaires

Table 5. Study Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow.Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin (2019)</td>
<td>4. Diagnosis was based on clinical signs and local pain alone. No imaging verification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gupta (2019)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scott (2019)</td>
<td>4. Study population may not be representative of intended use as it was focused on athletes, including some elite athletes</td>
<td>4. Not the intervention of interest as it included 6 weeks of supervised rehab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick</td>
<td>4. Key health outcomes not addressed</td>
<td>1. Not sufficient duration for benefit</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.


Table 6. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Follow Up</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin (2019)</td>
<td></td>
<td>1. Not blinded</td>
<td>1. Not registered</td>
<td>1. High amount of excluded data (38% for DASH at 12 mo); 6. Not intention to treat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gupta (2019)</td>
<td></td>
<td>1. Not registered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scott (2019)</td>
<td></td>
<td>1. Not registered</td>
<td></td>
<td>1. High loss to follow-up or missing data at 12 months (21%)</td>
<td>4. Underpowered</td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick (2019)</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.


Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference. 4. Underpowered

Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple intervals and/or p values not reported; 4. Comparative treatment effects not calculated
Section Summary: Platelet-Rich Plasma as a Primary Treatment of Tendinopathy
Multiple RCTs and systematic reviews with meta-analyses have evaluated the efficacy of PRP injections in individuals who have tendinopathy. The majority of the more recently-published systematic reviews and meta-analyses that only included RCTs failed to show a statistically and/or clinically significant impact on symptoms (ie, pain) or functional outcomes. Although 1 systematic review found statistically significantly lower pain scores at 12 months with platelet-rich plasma versus the comparators, its results should be interpreted with caution due to important study conduct limitations. Likewise, in subsequently published RCTs, although compared to a corticosteroid injection, 2 RCTs found platelet-rich plasma injection to result in significantly improved pain scores, important relevancy gaps and study conduct limitations exist that preclude reaching strong conclusions based on this evidence. Additionally, compared to placebo, platelet-rich plasma did not significantly improve pain after 12 months. Finally, compared with lidocaine, in individuals receiving platelet-rich plasma as an adjunct to ultrasound-guided tenotomy for recalcitrant elbow tendinopathy there were no significant differences in pain or disability outcomes.

PLATELET-RICH PLASMA AS A PRIMARY TREATMENT OF NON–TENDON SOFT TISSUE INJURY OR INFLAMMATION

Clinical Context and Therapy Purpose
The purpose of PRP injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, and anti-inflammatory agents, in patients with non-tendon soft tissue injury or inflammation (eg, plantar fasciitis).

The question addressed in this evidence review is: Does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest are individuals with non-tendon soft tissue injury or inflammation (eg, plantar fasciitis). Patients with non-tendon soft tissue injury or inflammation (eg, plantar fasciitis) are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting

Interventions
The therapy being considered is PRP injections. The use of PRP has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, and anti-inflammatory agents. These treatments are managed by orthopedic surgeons and primary care providers in an outpatient clinical setting.
Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life (QOL), and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for non-tendon soft tissue injury or inflammation (eg, plantar fasciitis) has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 2 years of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria
Methodologically credible studies were selected using the principles discussed under the first indication.

REVIEW OF EVIDENCE
Franceschi et al (2014) published a qualitative systematic review of the literature on PRP for chronic plantar fasciitis.(16) The literature search, conducted through June 2014, identified 8 prospective studies (N=256 patients), 3 of which were randomized. Most studies did not have a control group or report imaging evaluations as outcomes. Each study used a different device to prepare PRP. The 3 single-blinded RCTs (n=90 patients) compared PRP treatment with corticosteroids (n=60) or prolotherapy (n=30). Two trials reported statistically significant improvements with PRP and 1 trial reported no difference. The largest RCT (n=40) by Monto (2014) compared PRP with corticosteroid injection and had a follow-up to 24 months.(17) There was an apparent difference in age and baseline scores between the PRP and steroid groups. Blinded assessment using American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale scores at 3, 6, 12, and 24 months showed temporary improvements in the corticosteroid group, with a return to near-baseline levels (score, 58; scoring range, 0-100, with higher scores indicating less disability) by 12 months. In the PRP group, the AOFAS Ankle-Hindfoot Scale score increased from 37 at baseline to 95 at 3 months and remained elevated through 24 months, with a final score of 92 (difference of 46 from controls, p=0.001). Confirmation of these results in a larger double-blind RCT would permit greater certainty on the efficacy of PRP in plantar fasciitis.

Subsequent to the systematic review by Franceschi et al (2014), 3 additional randomized controlled trials have been published.(18,19,20) None were large double-blind RCT's of sufficient duration (i.e., 2 years) to conclusively demonstrate efficacy. The RCT's compared platelet-rich plasma treatment (total N=107) with corticosteroid injection (N=82) or saline injection (N=44). The platelet-rich plasma protocols differed across RCTs. The RCTs were small, ranging in size from 2820, to 155 participants.(18) Follow-up duration ranged from 6 months20, to 18 months. 19, Two were conducted in single centers in either the UK20, or India19, and the third was a multicenter RCT of 5 sites in the Netherlands.(20) None prespecified any methods to assess potential harms. Results were mixed across RCTs. The largest RCT (n=115) by Peerbooms et al (2019) compared platelet-rich plasma with corticosteroid injection and had a follow-up to 12 months.(18) In the RCT by Peerbooms et al (2019), the proportion of patients with at least a 25% improvement in Foot Function Index Pain Scores between baseline and 12 months was significantly greater in the platelet-rich plasma group (88.4% versus 55.6%; P=0.003). Additionally, mean Foot Function Index Disability Scores were significantly lower in the platelet-rich plasma group at 12 months (mean difference, 12.0; 95% CI, 2.3-21.6). But, these improvements did not translate into significantly greater quality of life in the platelet-rich plasma group. Also, important study design and conduct gaps exist that seriously limit the interpretation of these findings, including that
analysis excluded 29% of the randomized patients, which was less than the calculated sample size. Therefore, although evidence continues to develop, important uncertainties in efficacy and safety remain and larger double-blind RCT's are still needed.

Section Summary: Platelet-Rich Plasma as a Primary Treatment of Non-Tendon Soft Tissue Injury or Inflammation
Six small RCTs and multiple prospective observational studies have evaluated the efficacy of PRP injections in individuals with chronic plantar fasciitis. Preparation of PRP and outcome measures differed across studies. Results among the RCTs were inconsistent. The largest of the 3 RCTs showed that treatment using PRP compared with corticosteroid resulted in statistically significant but temporary improvements in pain and disability, but not quality of life. Larger RCTs are still needed to address important uncertainties in efficacy and safety, and to confirm these findings.

PLATELET-RICH PLASMA AS A PRIMARY TREATMENT OF OSTEOCHONDRAL LESIONS

Clinical Context and Therapy Purpose
The purpose of PRP injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, anti-inflammatory agents, and surgery in patients with osteochondral lesions.

The question addressed in this evidence review is: does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest are individuals with osteochondral lesions. Patients with osteochondral lesions are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

Interventions
The therapy being considered is PRP injections. The use of PRP has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, anti-inflammatory agents, and surgery. These treatments are managed by orthopedic surgeons and primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life (QOL), and treatment-related morbidity. The existing literature evaluating platelet-
rich plasma injections as a treatment for osteochondral lesions has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 28 weeks of follow-up is considered necessary to demonstrate efficacy.

**Study Selection Criteria**
Methodologically credible studies were selected using the principles discussed under the first indication.

**REVIEW OF EVIDENCE**
No RCTs on treatment of osteochondral lesions were identified. Mei-Dan et al (2012) reported a quasi-randomized study of 29 patients with 30 osteochondral lesions of the talus assigned to 3 intra-articular injections of hyaluronic acid or PRP. (21) At 28-week follow-up, scores on the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale score improved to a greater extent in the PRP group (from 68 to 92) than in the hyaluronic acid group (from 66 to 78) (p<0.05). Subjective global function also improved to a greater extent in the PRP group (from 58 to 91) than in the hyaluronic acid group (from 56 to 73). Interpretation of the composite measures of visual analog scale scores for pain and function is limited by differences between the groups at baseline. Also, neither the patients nor the evaluators were blinded to treatment in this small study.

**Section Summary: Platelet-Rich Plasma as a Primary Treatment of Osteochondral Lesions**
A single quasi-randomized study evaluated the efficacy of PRP injections in individuals who have osteochondral lesions. Compared with hyaluronic acid, treatment with PRP resulted in statistically significant improvements in AOFAS Ankle-Hindfoot Scale scores and global function, indicating improved outcomes. Adequately powered and blinded RCTs are required to confirm these findings.

**PLATELET-RICH PLASMA AS A PRIMARY TREATMENT OF KNEE OR HIP OSTEOARTHRITIS**

**Clinical Context and Therapy Purpose**
The purpose of PRP injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (eg, exercise, physical therapy), analgesics, anti-inflammatory agents, and surgery, in patients with knee or hip OA.

The question addressed in this evidence review is: does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICO was used to select literature to inform this review.

**Patients**
The relevant population of interest is individuals with knee or hip OA. Patients with knee or hip osteoarthritis are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.
Interventions
The therapy being considered is PRP injections. The use of PRP has been proposed as a
treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic
surgeries. The potential benefit of PRP has received considerable interest due to the appeal of
a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include nonpharmacologic therapy (eg, exercise, physical therapy),
analgesics, anti-inflammatory agents, and surgery. These treatments are managed by
orthopedic surgeons and primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures,
quality of life (QOL), and treatment-related morbidity. The existing literature evaluating platelet-
rich plasma injections as a treatment for knee or hip osteoarthritis has varying lengths of
follow-up, ranging from 6-12 months. While studies described below all reported at least one
outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 12
months of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first
indication

REVIEW OF EVIDENCE
A number of RCTs and several systematic reviews of RCTs evaluating use of PRP for knee
osteoarthritis (OA) have been published.(7,22,23,24,25,26,27,28) Protocols used in PRP
interventions for knee OA varied widely. For example, in the studies identified in the Laudy et
al (2015) systematic review, PRP was prepared using single, double, or triple spinning
techniques and interventions included between 1 and 3 injections delivered 1 to 3 weeks apart.
(22)

Systematic Reviews
In individuals with knee or hip osteoarthritis undergoing platelet-rich plasma injections, findings
from 4 systematic reviews are reported.(7,29,22,23) The systematic reviews have varied in
their outcomes of interest and their findings. Systematic reviews have generally found that
platelet-rich plasma was more effective than placebo or hyaluronic acid in reducing pain and
improving function. However, systematic review authors have noted that their findings should
be interpreted with caution due to important limitations including significant residual statistical
heterogeneity, questionable clinical significance, and high risk of bias in study conduct.

Johal et al (2019) conducted a systematic review and meta-analysis of RCTs comparing
platelet-rich plasma with hyaluronic acid (8 trials, N=927), or placebo (2 trials, N=105), or no
platelet-rich plasma (2 trials, N=123) or acetaminophen (1 trial, N=75), or a corticosteroid (1
trial, N=48).7, Meta-analysis showed that platelet-rich plasma was more effective than its
comparators at 12 months (standard mean difference, -0.91; 95% CI, -1.41 to -0.41). However,
the systematic review authors noted that important limitations of this finding included lack of a
clinically significant difference (i.e., less than the effect size threshold of 0.5 for a clinically
important difference), high residual statistical heterogeneity between studies (I²=89%) and high
risk of bias in study conduct.
Xu et al (2017) conducted a systematic review and meta-analysis of RCTs comparing PRP with hyaluronic acid (8 trials), or placebo (2 trials), for the treatment of knee OA (Table 7). (29) Risk of bias was assessed using Cochrane criteria. Four studies were assessed as having low quality, 3 as moderate quality, and 3 as high quality. Meta-analyses including 7 of the trials comparing PRP with hyaluronic acid showed that PRP significantly improved Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or International Knee Documentation Committee (IKDC) scores compared with HA at 6-month follow-up; however, when meta-analyses included only the 2 high-quality RCTs, there was not a significant difference between PRP and hyaluronic acid (Table 8). Also note that the Western Ontario and McMaster Universities Osteoarthritis Index evaluates 3 domains: pain, scored from 0-20; stiffness, scored from 0-8; and physical function, scored from 0-68. Higher scores represent greater pain and stiffness as well as worsened physical capability. The IKDC is a patient-reported, knee-specific outcome measure that measures pain and functional activity. In the meta-analysis comparing PRP with placebo, a third trial was included, which had four treatment groups, two of which were PRP and placebo. This analysis showed that PRP significantly improved WOMAC or IKDC scores compared with placebo; however, only one of the trials was considered high quality and that trial only enrolled 30 patients. All meta-analyses showed high heterogeneity among trials (I² ≥ 90%).

Laudy et al (2015) conducted a systematic review of RCTs and nonrandomized clinical trials to evaluate the effect of PRP on patients with knee OA (Table 7). (22) Ten trials (N=1110 patients) were selected. Cochrane criteria for risk of bias were used to assess study quality, with 1 trial rated as having a moderate risk of bias and the remaining 9 trials as high risk of bias. While meta-analyses showed that PRP was more effective than placebo or hyaluronic acid in reducing pain and improving function (Table 8), larger randomized studies with lower risk of bias are needed to confirm these results.

Chang et al 2014 published a systematic review that included 5 RCTs, 3 quasi-randomized controlled studies, and 8 single-arm prospective series (N=1543 patients) (Table 4). (23) The Jadad scale was used to assess RCTs, and the Newcastle-Ottawa Scale was used to assess the other studies; however, results of the quality assessments were not reported. Meta-analysis of functional outcomes at 6 months found that the effectiveness of PRP (effect size, 1.5; 95% CI, 1.0 to 2.1) was greater than that of hyaluronic acid (effect size, 0.7; 95% CI, 0.6 to 0.9; when only RCTs were included). However, there was no significant difference at 12-month follow-up between PRP (effect size, 0.9; 95% CI, 0.5 to 1.3) and hyaluronic acid (effect size, 0.9; 95% CI, 0.5 to 1.2; when only RCTs were included). Fewer than 3 injections, single spinning, and lack of additional activators led to greater uncertainty in the treatment effects. PRP also had lower efficacy in patients with higher degrees of cartilage degeneration. Results were consistent when analyzing only RCTs, but asymmetry in funnel plots suggested significant publication bias.

Table 7. Systematic Review Characteristics for Knee or Hip Osteoarthritis

<table>
<thead>
<tr>
<th>Study</th>
<th>Search Date</th>
<th>Trials</th>
<th>Participants</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johal et al (2019)</td>
<td>Feb 2017</td>
<td>8 PRP vs HA</td>
<td>Patients with knee OA</td>
<td>14 RCTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 PRP vs placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 PRP vs no PRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 PRP vs corticosteroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 PRP vs acetaminophen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xu et al (2017)</td>
<td>May 2016</td>
<td>8 PRP vs HA</td>
<td>Patients with knee OA</td>
<td>10 RCTs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Laudy et al (2015) 22  Jun 2014  8 PRP vs HA  1 PRP vs placebo  1 PRP, different preparations  Patients with knee OA  6 RCTs  4 nonrandomized

Chang et al (2014) 23  Sep 2013  6 PRP vs HA  1 PRP vs placebo  1 PRP, different preparations  8 single-arm PRP  Patients with knee OA  5 RCTs  3 quasi-randomized  8 single-arm

Table 8. Systematic Review Results for Knee or Hip Osteoarthritis

<table>
<thead>
<tr>
<th>Study</th>
<th>Change in Functional Scores (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 Months</td>
</tr>
<tr>
<td>Xu et al (2017) 29</td>
<td>PRP vs HA:</td>
</tr>
<tr>
<td></td>
<td>All trials: -0.9 (-1.4 to -0.3)</td>
</tr>
<tr>
<td></td>
<td>Low quality: -13.3 (-33.9 to 3.7)</td>
</tr>
<tr>
<td></td>
<td>Moderate quality: -1.3 (-1.6 to -1.0)</td>
</tr>
<tr>
<td></td>
<td>High quality: -0.1 (-0.3 to 0.1)</td>
</tr>
<tr>
<td></td>
<td>PRP vs placebo:</td>
</tr>
<tr>
<td></td>
<td>All trials (3): -2.1 (-3.3 to -1.0)</td>
</tr>
<tr>
<td>Laudy et al (2015) 22</td>
<td>PRP vs HA: -0.8 (-1.0 to -0.6)</td>
</tr>
<tr>
<td>Chang et al (2014) 23</td>
<td>PRP, baseline vs post-treatment:</td>
</tr>
<tr>
<td></td>
<td>All studies: 2.5 (1.9 to 3.1)</td>
</tr>
<tr>
<td></td>
<td>Single-arm: 3.1 (2.0 to 4.1)</td>
</tr>
<tr>
<td></td>
<td>Quasi-randomized: 3.1 (1.4 to 3.8)</td>
</tr>
<tr>
<td></td>
<td>RCT: 1.5 (1.0 to 2.1)</td>
</tr>
<tr>
<td></td>
<td>PRP, baseline vs posttreatment:</td>
</tr>
<tr>
<td></td>
<td>All studies: 2.9 (1.0 to 4.8)</td>
</tr>
<tr>
<td></td>
<td>Single-arm: 2.6 (-0.4 to 5.7)</td>
</tr>
<tr>
<td></td>
<td>Quasi-randomized: 4.5 (4.1 to 5.0)</td>
</tr>
<tr>
<td></td>
<td>RCT: 0.9 (0.5 to 1.3)</td>
</tr>
</tbody>
</table>

CI: confidence interval; HA: hyaluronic acid; NR: not reported; PRP: platelet-rich plasma; RCT: randomized controlled trial; OA: osteoarthritis.

Randomized Controlled Trials

In individuals with knee osteoarthritis undergoing platelet-rich plasma injections, 3 RCTs with follow-up durations of at least 12 months have been published subsequent to the above-described systematic reviews (Tables 9-12).(30,31,32) All were conducted outside of the United States. Sample sizes ranged from 87 to 192 participants. Comparator treatments included hyaluronic acid in all 3 RCTs, and corticosteroids or placebo in 2 RCTs. Two of the RCTs found statistically significantly greater 12-month reductions in the Western Ontario and McMaster Universities Osteoarthritis Index scores with platelet-rich plasma versus the comparator treatments.30,32, However, these findings should be interpreted with caution due to important study conduct limitations, including potential inadequate control for selection bias and unclear blinding. Additionally, no significant differences between platelet-rich plasma and hyaluronic acid were found in the International Knee Documentation Committee (IKDC) subjective score or EuroQol visual analog scale score in the longest-term trial with 5 years of follow-up.(31) In the RCT by Di Martino et al (2019) reintervention rates were significantly lower with platelet-rich plasma compared with hyaluronic acid at the 24-month follow-up assessment (22.6% 37.1%; P=0.036), but the difference was not maintained at 5 years.

Dallari et al (2016) reported on results of an RCT that compared PRP with hyaluronic acid alone or combination PRP plus hyaluronic acid in 111 patients with hip OA.(33) Although this well-conducted RCT reported positive results, with statistically significant reductions in VAS scores (lower scores imply less pain) at 6 months in the PRP arm (21; 95% CI, 15 to 28) versus the hyaluronic acid arm (35; 95% CI, 26 to 45) or the PRP plus hyaluronic acid arm (44; 95% CI, 36 to 52), the impact of treatment on other secondary outcome measures such as
Harris Hip Score and WOMAC scores was not observed. Notably, there was no control for type I error for multiple group comparisons at different time points, and the trial design did not incorporate a sham-control arm.

Trueba Vasavilbaso et al (2017) conducted a controlled trial that randomized patients after knee arthroscopy to 5 injections of Suprahyl/Adant (n=10), 4 injections of Orthovisc (n=10), 3 injections of Synvisc (n=10), 1 injection of PRP (n=10), or standard of care (n=10).(34) All patients received the same rehabilitation protocol. At 18-month follow-up, total WOMAC scores improved most from baseline with Suprahyl/Adant (65% reduction). The next best improvement was seen with PRP (55% reduction), then Synvisc (50% reduction), and Orthovisc (30% reduction). The control group experienced a 15% increase in WOMAC scores.

Table 9. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2016)</td>
<td>Italy</td>
<td>NR</td>
<td>2010-2011</td>
<td>Patients with hip OA</td>
<td>PRP (n=44)</td>
<td>PRP+HA (n=31) HA (n=36)</td>
</tr>
<tr>
<td>Trueba Vasavilbaso (2017)</td>
<td>Mexico</td>
<td>1</td>
<td>2013-2014</td>
<td>Patients with meniscal pathology and knee OA, following knee arthroscopic</td>
<td>PRP (N=10)</td>
<td>5 injections of Suprahyl/Adant (n=10) OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>debridement</td>
<td></td>
<td>4 injections of Orthovisc (n=10) OR Comparator 3=3 injections of Synvisc (n=10) OR Comparator 4=Standard Care</td>
</tr>
<tr>
<td>Huang (2019)</td>
<td>China</td>
<td>NR</td>
<td>2016-2017</td>
<td>Patients with knee OA</td>
<td>PRP (N=40)</td>
<td>HA (N=40) CS (N=40)</td>
</tr>
<tr>
<td>Di Martino (2019)</td>
<td>Italy</td>
<td>1</td>
<td>2009-2013</td>
<td>Patients with knee OA</td>
<td>PRP (N=96)</td>
<td>HA (N=96)</td>
</tr>
</tbody>
</table>

HA: hyaluronic acid; RCT: randomized controlled trial; OA: osteoarthritis; PRP: platelet-rich plasma; NR: not reported.

Table 10. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>VAS Score</th>
<th>Change in WOMAC Scores from Baseline</th>
<th>General Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2016)</td>
<td>6 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRP+HA</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HA</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trueba Vasavilbaso et al (2017)</td>
<td>% reduction at 18 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td>-55%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suprahyl/Adant</td>
<td>-65%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synvisc</td>
<td>-50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Intervention</td>
<td>Comparator</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------</td>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Dallari (2016)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trueba Vasavilbaso et al (2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang (2019)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Di Martino (2019)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lin (2019)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

a. Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b. Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

c. Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.


<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Binding&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Selective Reporting&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Follow Up&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Power&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Statistical&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2016)&lt;sup&gt;33&lt;/sup&gt;</td>
<td>2. Allocation not concealed from patients or health care providers</td>
<td>1. Only data collectors and outcome assessors blinded to treatment assignment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trueba Vasavilbaso et al (2017)&lt;sup&gt;34&lt;/sup&gt;</td>
<td>3. Inadequate control for selection bias: Orthovisc® group older than Synvisc® group (71.1 y vs 56.9 y; P=0.007)</td>
<td>1. Patients not blinded to treatment assignment</td>
<td>1. Not registered</td>
<td>6. Not intention to treat</td>
<td>1. Power not calculated</td>
<td></td>
</tr>
<tr>
<td>Di Martino (2019)&lt;sup&gt;31&lt;/sup&gt;</td>
<td>4. Inadequate control for selection bias - PRP group younger (52.7y vs 57.5y; p=0.014)</td>
<td>1. Unblinded to treatment after first year</td>
<td>6. Not intent to treat (excluded 13%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin (2019)&lt;sup&gt;32&lt;/sup&gt;</td>
<td>4. Inadequate control for selection bias - greater BMI in HA group (26.26) vs PRP (23.96), P=0.0127</td>
<td></td>
<td>1. Not registered</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.


<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

**Section Summary: Platelet-Rich Plasma as a Primary Treatment of Knee or Hip Osteoarthritis**

Multiple RCTs and systematic reviews with meta-analysis have evaluated the efficacy of PRP injections in individuals with knee or hip OA. Most trials have compared PRP with hyaluronic acid for knee OA. A single RCT compared PRP with hyaluronic acid alone or combination PRP plus hyaluronic acid in hip OA. Systematic reviews have generally found that platelet-rich plasma was more effective than placebo or hyaluronic acid in reducing pain and improving function. However, systematic review authors have noted that their findings should be interpreted with caution due to important limitations including significant residual statistical heterogeneity, questionable clinical significance, and high risk of bias in study conduct. RCTs with follow-up durations of at least 12 months published subsequent to the systematic reviews found statistically significantly greater 12-month reductions in the Western Ontario and McMaster Universities Osteoarthritis Index scores, but these findings were also limited by important study conduct flaws including potential inadequate control for selection bias and unclear blinding. Also, benefits were not maintained at 5 years. Also, using hyaluronic acid as
a comparator is questionable, because the evidence demonstrating the benefit of hyaluronic acid treatment for osteoarthritis is not robust. The single RCT evaluating hip osteoarthritis reported statistically significant reductions in visual analog scale scores but no significant differences in Harris Hip Score and the Western Ontario and McMaster Universities Osteoarthritis Index scores. Additional larger controlled studies comparing platelet-rich plasma with placebo and alternatives other than hyaluronic acid are needed to determine the efficacy of platelet-rich plasma for knee and hip osteoarthritis. Further studies are also needed to determine the optimal protocol for delivering platelet-rich plasma.

**PLATELET-RICH PLASMA AS AN ADJUNCT TO SURGERY**

**Anterior Cruciate Ligament Reconstruction**

**Clinical Context and Therapy Purpose**

The purpose of PRP injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in patients with anterior cruciate ligament (ACL) reconstruction.

The question addressed in this evidence review is: Does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICO was used to select literature to inform this review.

**Patients**

The relevant population of interest is individuals with ACL reconstruction. Patients with anterior cruciate ligament (ACL) reconstruction are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

**Interventions**

The therapy being considered is PRP injections plus orthopedic surgery. The use of PRP has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

**Comparators**

Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

**Outcomes**

The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life (QOL), morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for ACL reconstruction has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, two years of follow-up is considered necessary to demonstrate efficacy.
Study Selection Criteria
Methodologically credible studies were selected using the principles discussed under the first indication.

REVIEW OF EVIDENCE
A Cochrane review by Moraes et al (2013) on platelet-rich therapies for musculoskeletal soft tissue injuries identified 2 RCTs and 2 quasi-randomized studies (N=203 patients) specifically on PRP used in conjunction with ACL reconstruction.(35) Pooled data found no significant difference in IKDC scores between the PRP and control groups.

A qualitative, systematic review by Figueroa et al (2015) included 11 RCTs or prospective cohort studies (N=516 patients).(36) Four studies found significantly faster graft maturation while 3 found no significant difference. One study showed faster tunnel healing while 5 showed no benefit. One study showed better clinical outcomes while 5 showed no improvement in clinical outcomes when using PRP.

The largest RCT, reported by Nin et al (2009), randomized 100 patients to arthroscopic ACL reconstruction with or without PRP.(37) The use of PRP on the graft and inside the tibial tunnel in patients treated with bone-patellar tendon-bone allografts had no discernible clinical or biomechanical effect at 2-year follow-up.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment of Anterior Cruciate Ligament Reconstruction
Two systematic reviews that included multiple RCTs, quasi-randomized studies, and prospective studies have evaluated the efficacy of PRP injections in individuals undergoing ACL reconstruction. Only 1 of the 2 systematic reviews conducted a meta-analysis, which showed that adjunctive PRP treatment did not result in a significant effect on IKDC score. Individual studies have shown mixed results.

Hip Fracture
Clinical Context and Therapy Purpose
The purpose of PRP injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in patients with hip fracture.

The question addressed in this evidence review is: Does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is individuals with hip fracture. Patients with hip fracture are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.
Interventions
The therapy being considered is PRP injections plus orthopedic surgery. The use of PRP has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life (QOL), morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for hip fracture has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

REVIEW OF EVIDENCE
One RCT was identified for treatment of hip fracture with PRP. Griffin et al (2013) reported a single-blind randomized trial assessing the use of PRP for the treatment of hip fractures in patients ages 65 years and older.(38) Patients underwent internal fixation of a hip fracture with cannulated screws and were randomized to standard-of-care fixation (n=99) or standard-of-care fixation plus injection of PRP into the fracture site (n=101). The primary outcome measure was the failure of fixation within 12 months, defined as any revision surgery. The overall risk of revision by 12 months was 36.9%, and the risk of death was 21.5%. There was no significant risk reduction (39.7% control versus 34.1% PRP; absolute risk reduction, 5.6%; 95% CI, -10.6% to 21.8%) or significant difference between groups for most of the secondary outcome measures. For example, mortality was 23% in the control group and 20% in the PRP group. The length of stay was significantly reduced in the PRP-treated group (median difference, 8 days). For this measure, there is a potential for bias from the nonblinded treating physician.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Hip Fracture
A single open-labeled RCT has evaluated the efficacy of PRP injections in individuals with hip fracture. This trial failed to show any statistically significant reductions in the need for revision surgery after PRP treatment.

Long-Bone Nonunion

Clinical Context and Therapy Purpose
The purpose of PRP injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as Recombinant human bone morphogenous protein-7 (rhBMP-7) plus orthopedic surgery, in patients with long bone nonunion.
The question addressed in this evidence review is: Does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICO was used to select literature to inform this review.

**Patients**
The relevant population of interest is individuals with long bone nonunion. Patients with long bone nonunion are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

**Interventions**
The therapy being considered is PRP injections plus orthopedic surgery. The use of PRP has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

**Comparators**
Comparators of interest include rhBMP-7 plus orthopedic surgery. This is performed by an orthopedic surgeon in an outpatient clinical setting.

**Outcomes**
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life (QOL), morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for long bone nonunion has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

**Study Selection Criteria**
Methodologically credible studies were selected using the principles described in the first indication.

**REVIEW OF EVIDENCE**
A Cochrane review by Griffin et al (2012) found only 1 small RCT (n=21) evaluating PRP for long-bone healing.(39) However, because only studies comparing PRP with no additional treatment or a placebo were eligible for inclusion, reviewers did not select a larger RCT by Calori et al (2008; discussed below).(40)

The trial study by Dallari et al (2007), which was included in the Cochrane review, compared PRP plus allogenic bone graft with allogenic bone graft alone in patients undergoing corrective osteotomy for medial compartment osteoarthrosis of the knee.(41) According to Cochrane reviewers, the risk of bias in this study was substantial. Results showed no significant differences in patient-reported or clinician-assessed functional outcome scores between groups at 1 year. However, the proportion of bones united at 1 year was statistically significantly higher in the PRP plus allogenic bone graft arm (8/9) compared with the allogenic bone graft alone arm (3/9; relative risk, 2.67; 95% CI, 1.03 to 6.91). This benefit, however, was
not statistically significant when assuming poor outcomes for participants who were lost to follow-up (8/11 versus 3/10; relative risk, 2.42; 95% CI, 0.88 to 6.68).

Calori et al (2008) compared application of PRP with rhBMP-7 for the treatment of long-bone nonunions in an RCT involving 120 patients and 10 surgeons. (40) Inclusion criteria were posttraumatic atrophic nonunion for at least 9 months, with no signs of healing over the last 3 months, and considered as treatable only by means of fixation revision. Autologous bone graft had been used in a prior surgery in 23 cases in the rhBMP-7 group and 21 cases in the PRP group. Computer-generated randomization created 2 homogeneous groups; there were generally similar numbers of tibial, femoral, humeral, ulnar, and radial nonunions in the 2 groups. Following randomization, patients underwent surgery for nonunion, including bone grafts according to the surgeon’s choice (66.6% of rhBMP-7 patients, 80% of PRP patients). Clinical and radiologic evaluations by 1 radiologist and 2 surgeons trained in the study protocol revealed fewer unions in the PRP group (68%) than in the rhBMP-7 group (87%). Clinical and radiographic healing times were also found to be slower by 13% to 14% with PRP.

Samuel et al (2017) conducted a controlled trial in which patients with delayed unions (15-30 weeks old) were randomized to 2 PRP injections at the fracture site at baseline and 3 weeks (n=23) or no treatment (n=17). (42) The delayed unions were in the tibia (n=29), femur (n=8), forearm (n=2), and the humerus (n=1). The main outcome was long bone union, defined as no pain or tenderness on weight bearing, no abnormal mobility, and bridging at 3 or more cortices in x-ray. Examinations were conducted every 6 weeks for 36 weeks or until union. Percent union did not differ significantly between the 2 groups (78% in the PRP group versus 59% in the control group). Time to union also did not differ significantly (15.3 weeks for the PRP group versus 13.1 weeks for the control group).

### Table 13. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2007)</td>
<td>Italy</td>
<td>NR</td>
<td>NR</td>
<td>Patients undergoing high tibial osteotomy to treat genu varum</td>
<td>Active</td>
<td>Comparator 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Implantation of lyophilized bone chips with platelet gel (n=11)</td>
<td>PRP (n=60)</td>
<td>Implantation of lyophilized bone chips with platelet gel and bone marrow stromal cells (n=12)</td>
</tr>
<tr>
<td>Calori (2008)</td>
<td>Italy</td>
<td>1</td>
<td>2005-2007</td>
<td>Patients undergoing treatment of long bone nonunions</td>
<td>PRP (n=60)</td>
<td></td>
</tr>
<tr>
<td>Samuel (2017)</td>
<td>India</td>
<td>1</td>
<td>2010-2014</td>
<td>Patients with delayed unions</td>
<td>PRP (n=23)</td>
<td>No treatment (n=17)</td>
</tr>
</tbody>
</table>

hBMP-7: recombinant human bone morphogenetic protein-7; RCT: randomized controlled trial; PRP: platelet-rich plasma; NR: not reported.

### Table 14. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Knee Society Score at 1 yr</th>
<th>Knee Society Functional Score at 1 yr</th>
<th>Union Rate</th>
<th>Median Healing Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2007)</td>
<td>91.3 +/- 2</td>
<td>99.0 +/- 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td>89.9 +/- 4</td>
<td>99.2 +/- 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-PRP</td>
<td>90.3 +/- 4</td>
<td>98.8 +/- 0.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 15. Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2007) 41</td>
<td>4. Only 33 patients included</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calori (2008) 40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samuel (2017) 42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

- **Population key**: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
- **Intervention key**: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
- **Comparator key**: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
- **Outcomes key**: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
- **Follow-Up key**: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

### Table 16. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Follow Up</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2007) 41</td>
<td>3. Allocation concealment unclear</td>
<td>1,2,3. No blinding described</td>
<td>1,2,3. No blinding described</td>
<td>1.2. Study was underpowered and nonparametric statistical tests were performed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calori (2008) 40</td>
<td>2. Allocation not concealed</td>
<td>1,2,3. No blinding described</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samuel (2017) 42</td>
<td>1. Randomization procedure not described, 3. Allocation concealment unclear</td>
<td>1,2,3. No blinding described</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

- **Blinding key**: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Long Bone Nonunion

Three RCTs have evaluated the efficacy of PRP injections in individuals with long bone nonunion. One trial with a substantial risk of bias failed to show significant differences in patient-reported or clinician-assessed functional outcome scores between patients who received PRP plus allogenic bone graft versus those who received only the allogenic bone graft. While the trial showed statistically significant increases in the proportion of bones that healed in patients receiving PRP in a modified intention-to-treat, the results did not differ in the intention-to-treat analysis. A RCT which compared PRP with rhBMP-7 also failed to show any clinical and radiologic benefits of PRP over rhBMP-7. The third RCT found no difference in a number of unions or time to union in patients receiving PRP injections or no treatment.

Rotator Cuff Repair

Clinical Context and Therapy Purpose
The purpose of PRP injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in patients with rotator cuff repair.

The question addressed in this evidence review is: Does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is individuals with rotator cuff repair. Patients with rotator cuff repair are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

Interventions
The therapy being considered is PRP injections plus orthopedic surgery. The use of PRP has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.
Outcomes

The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life (QOL), morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for rotator cuff repair has varying lengths of follow-up, ranging from 6 months to 3.5 years. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 3.5 years of follow-up is considered necessary to demonstrate efficacy.

Study Selection Criteria

Methodologically credible studies were selected using the principles described in the first indication.

REVIEW OF EVIDENCE

The literature on PRP for rotator cuff repair consists of several RCTs and systematic reviews that have evaluated the efficacy of PRP membrane or matrix combined with surgical repair of the rotator cuff.

The systematic reviews have varied in their outcomes of interest and findings (Tables 17 and 18).(43,7,35,44,45,46) For pain outcomes, systematic reviews consistently found significant reductions with platelet-rich plasma at 12 months.(47,43,7) However, systematic review authors noted that the pain findings should be interpreted with caution due to significant residual statistical heterogeneity (47), lack of a clinically significant difference (ie, less than the effect size threshold of 0.5 for a clinically important difference) (7), and high risk of bias in study conduct.(7) Additionally, the 12-month pain reduction with platelet-rich plasma was not maintained in RCTs with longer-term follow-up of 24 months or longer.(43) Systematic reviews generally did not show a statistically or clinically significant benefit of platelet-rich plasma on other outcomes, including function, retear rate and Constant scores. No reviews have demonstrated a consistent statistical and clinical significant benefit of platelet-rich plasma across multiple outcomes of interest for the 3.5 years of follow-up that is considered necessary to conclusively demonstrate efficacy. The systematic review by Wang et al (2019) reported on adverse effects. Wang et al (2019) (43) reported that complications were only reported in 1 of the included RCTs, occurring in 5.6% of participants in the platelet-rich plasma groups and none in the control groups. The complications included infection, hematoma, and an exantheimatous itchy skin lesion in 1 patient each.

Table 17. Systematic Reviews & Meta-Analysis Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen (2017)47</td>
<td>2011-2016</td>
<td>37</td>
<td>Patients with tendon and ligament injuries</td>
<td>1031a (NR)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Study</td>
<td>Year Range</td>
<td>N</td>
<td>Diagnosis</td>
<td>No. Participants</td>
<td>Study Type</td>
<td>Treatment</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------</td>
<td>----</td>
<td>-----------------------------------------------</td>
<td>------------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Fu (2017)</td>
<td>2011-2015</td>
<td>11</td>
<td>Patients with rotator cuff injury or tendinopathy</td>
<td>638 (NR)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Zhao (2015)</td>
<td>2011-2013</td>
<td>8</td>
<td>Patients with rotator cuff injury</td>
<td>464 (28-88)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Moraes (2013)</td>
<td>2008-2013</td>
<td>19</td>
<td>Patients undergoing rotator cuff repair</td>
<td>1088 (23-150)</td>
<td>RCT and quasi-randomized trials</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: not reported; RCT: randomized controlled trial.
aNumber of participants from the 21 articles which could be included in the quantitative analysis.

### Table 18. Systematic Reviews & Meta-Analysis Results

<table>
<thead>
<tr>
<th>Study</th>
<th>VAS Reduction at 1 Year</th>
<th>VAS Change from Pre- to Post-treatment</th>
<th>Difference in Retear Rate</th>
<th>Difference in Function at 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johal (2019)</td>
<td>7 RCTs, N=324</td>
<td>0.261</td>
<td>0.29</td>
<td>0.38</td>
</tr>
<tr>
<td>Wang (2019)</td>
<td>5 RCTs; N=338</td>
<td>0.41</td>
<td>RR for 1-year: 0.29 RR ≥ 2-year: 0.96</td>
<td>0.38</td>
</tr>
<tr>
<td>Chen (2017)</td>
<td>WMD -0.84</td>
<td>-1.23 to -0.44</td>
<td>1-year: 0.13, 0.65 ≥ 2-year: 0.52, 1.78</td>
<td>0.16, 0.60</td>
</tr>
<tr>
<td>Fu (2017)</td>
<td>SMD 0.142</td>
<td>0.08 to 0.364</td>
<td>0.209</td>
<td>0.25</td>
</tr>
<tr>
<td>Zhao (2015)</td>
<td>RR 0.94</td>
<td>0.70 to 1.25</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Moraes (2013)</td>
<td>SMD 0.25</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Randomized Controlled Trials
Three small, single-center RCTs have been published subsequent to the systematic reviews described above. (49, 50, 51) Walsh et al (2018) published a prospective, randomized, single-blinded study evaluating platelet-rich plasma in fibrin matrix as a means to augment rotator cuff repair. (49) Malavolta et al (2018) published 5-year clinical and structural evaluations in follow-up to their 2014 publication of their 24-month results. (50) In contrast to previous RCT’s that have focused on administration of platelet-rich plasma at the time of rotator cuff repair surgery, the third RCT, published by Snow et al (2019) (51) was unique in publishing a randomized double-blind trial of delayed delivery of platelet-rich plasma at 10-15 days post-surgery. Sample sizes ranged from 51 patients (50) to 97 patients. (51) Results of these 3 RCTs are consistent with the systematic reviews in finding no statistically or clinically significant benefit of platelet-rich plasma on multiple outcomes.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Rotator Cuff Repair
For individuals undergoing rotator cuff repair who receive platelet-rich plasma injections, the evidence includes multiple RCTs and systematic reviews with meta-analyses. Relevant outcomes include symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Although systematic reviews consistently found significant reductions in pain with platelet-rich plasma at 12 months, important study conduct and relevance weaknesses limit interpretation of these findings. Additionally, the pain reductions with platelet-rich plasma were not maintained in longer-term studies. Further, the systematic reviews and meta-analyses failed to show a statistically and/or clinically significant impact on other outcomes. Findings of subsequently published small, single-center RCTs were consistent with the systematic reviews. The variability in platelet-rich plasma preparation techniques and platelet-rich plasma administration limit the generalizability of the studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Spinal Fusion
Clinical Context and Therapy Purpose
The purpose of PRP injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in patients with spinal fusion.

The question addressed in this evidence review is: Does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICO was used to select literature to inform this review.

<table>
<thead>
<tr>
<th>95% CI</th>
<th>-0.07 to 0.57</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-value</td>
<td>0.12</td>
</tr>
</tbody>
</table>

1 Scales used were not specified. Study authors noted, “If data were provided on more than 1 scale for pain, only the most commonly reported scales, across included studies (for which complete data were available) were combined.”
RR: risk ratio; SMD: standard mean difference; WMD: weighted mean difference; VAS: visual analog scale; CI: confidence interval; UCLA: University of California at Los Angeles (UCLA) activity score
Patients
The relevant population of interest is individuals with spinal fusion. Patients with spinal fusion are actively managed pre- and postoperatively by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

Interventions
The therapy being considered is PRP injections plus orthopedic surgery. The use of PRP has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life (QOL), morbidity events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for spinal fusion has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

REVIEW OF EVIDENCE
One small (N=62), unblinded, single-center RCT for spinal fusion conducted in Japan and published by Kubota et al (2019) was identified that compared platelet-rich plasma to no platelet-rich plasma. Follow-up was 24 months. Although fusion rates were significantly improved with platelet-rich plasma, there were no significant differences in visual analog scale scores between the 2 groups. Major limitations of this RCT include that patients were unblinded to treatment and there was no placebo comparator.

Two prospective observational studies found no differences in fusion rates with use of a platelet gel or platelet glue compared with historical controls.

Subsection Summary: Spinal Fusion
For individuals undergoing spinal fusion who receive platelet-rich plasma injections, the evidence includes a single small RCT and two observational studies. Relevant outcomes include symptoms, functional outcomes, health status measures, quality of life, morbidity events, resource utilization, and treatment-related morbidity. Studies have generally failed to show a statistically and/or clinically significant impact on symptoms (ie, pain). The evidence is insufficient to determine the effects of the technology on health outcomes.
Subacromial Decompression Surgery

Clinical Context and Therapy Purpose
The purpose of PRP injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in patients with subacromial decompression surgery.

The question addressed in this evidence review is: Does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest are individuals with subacromial decompression surgery. Patients with subacromial decompression surgery are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

Interventions
The therapy being considered is PRP injections plus orthopedic surgery. The use of PRP has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life (QOL), morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for subacromial decompression surgery has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

REVIEW OF EVIDENCE
One small RCT evaluated the use of PRP as an adjunct to subacromial decompression surgery. Everts et al (2008) reported on a rigorously conducted, small (n=40) double-blinded RCT of platelet and leukocyte-rich plasma gel following open subacromial decompression surgery in a carefully selected patient population.(55) Neither self-assessed nor physician-assessed instability improved. Both subjective pain and use of pain medication were lower in the platelet and leukocyte-rich plasma group across the 6 weeks of measurements. For example, at 2 weeks after surgery, VAS scores for pain were lower by about 50% in the PLRP
group (close to 4 in the control group, close to 2 in the PLRP group), and only 1 (5%) patient in
the PLRP group was taking pain medication compared with 10 (50%) control patients. Objective measures of range of motion showed clinically significant improvements in the PLRP group across the 6-week assessment period, with patients reporting improvements in activities of daily living, such as the ability to sleep on the operated shoulder at 4 weeks after surgery and earlier return to work.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Subacromial Decompression Surgery
A single small RCT has evaluated the efficacy of PRP injections in individuals undergoing subacromial decompression surgery. Compared with controls, PRP treatment did not improve self-assessed or physician-assessed instability. However, subjective pain, use of pain medication, and objective measures of range of motion showed clinically significant improvements with PRP. Larger RCTs would be required to confirm these benefits.

Total Knee Arthroplasty

Clinical Context and Therapy Purpose
The purpose of PRP injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in patients with TKA.

The question addressed in this evidence review is: Does the use of PRP improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is individuals with TKA. Patients with total knee arthroplasty are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

Interventions
The therapy being considered is PRP injections plus orthopedic surgery. The use of PRP has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for total knee arthroplasty has varying lengths of follow-up. While studies described below all
reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

REVIEW OF EVIDENCE
Morishita et al (2014) reported on the results of a controlled trial of 40 patients, scheduled for unilateral total knee arthroplasty, who were randomized to intraoperative PRP (n=20) or no additional intraoperative treatment (n=20). There were no significant differences between the PRP and untreated control groups in bleeding, range of motion, swelling around the knee joint, muscle power recovery, pain, Knee Society Scores, or Knee Injury and Osteoarthritis Outcome Score.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Total Knee Arthroplasty
A single small RCT has evaluated the efficacy of PRP injections in individuals undergoing total knee arthroplasty. There were no significant differences between the PRP and untreated control groups across several functional and pain outcomes.

SUMMARY OF EVIDENCE
Primary Treatment for Tendinopathies
For individuals with tendinopathy who receive PRP injections, the evidence includes multiple RCTs and systematic reviews with meta-analyses. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Findings from meta-analyses of RCTs have been mixed and have generally found that PRP did not have a statistically and/or clinically significant impact on symptoms (ie, pain) or functional outcomes. Findings from subsequently published RCTs have also been mixed. In RCTs that have found significantly improved pain outcomes for platelet-rich plasma injections, important relevancy gaps and study conduct limitations preclude reaching strong conclusions based on their findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

Primary Treatment for Non-Tendon Soft Tissue Injury or Inflammation
For individuals with non-tendon soft tissue injury or inflammation (eg, plantar fasciitis) who receive PRP injections, the evidence includes 6 small RCTs, multiple prospective observational studies, and a systematic review. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The systematic review, which identified 3 RCTs on PRP for plantar fasciitis, did not pool study findings. Results among the 6 RCTs were inconsistent. The largest RCT showed that treatment using PRP compared with corticosteroid injection resulted in statistically significant improvement in pain and disability, but not quality of life. Larger RCTs are still needed to address important uncertainties in efficacy and safety. The evidence is insufficient to determine the effects of the technology on health outcomes.

Primary Treatment for Osteochondral Lesions
For individuals with osteochondral lesions who receive PRP injections, the evidence includes an open-labeled quasi-randomized study. Relevant outcomes are symptoms, functional
outcomes, health status measures, quality of life, and treatment-related morbidity. The quasi-randomized study found a statistically significant greater impact on outcomes in the PRP group than in the hyaluronic acid group. Limitations of the evidence base include lack of adequately randomized studies, lack of blinding, lack of sham controls, and comparison only to an intervention of uncertain efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Primary Treatment for Knee or Hip Osteoarthritis**
For individuals with knee or hip OA who receive PRP injections, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Most trials have compared PRP with hyaluronic acid for knee OA. Systematic reviews have generally found that platelet-rich plasma was more effective than placebo or hyaluronic acid in reducing pain and improving function. However, systematic review authors have noted that their findings should be interpreted with caution due to important limitations including significant residual statistical heterogeneity, questionable clinical significance, and high risk of bias in study conduct. RCTs with follow-up durations of at least 12 months published subsequent to the systematic reviews found statistically significantly greater 12 month reductions in the Western Ontario and McMaster Universities Osteoarthritis Index scores, but these findings were also limited by important study conduct flaws including potential inadequate control for selection bias and unclear blinding; and, benefits were not maintained at 5 years. Also, using hyaluronic acid as a comparator is questionable, because the evidence demonstrating the benefit of hyaluronic acid treatment for OA is not robust. The single RCT evaluating hip OA reported statistically significant reductions in visual analog scale scores for pain, with no difference in functional scores. Additional studies comparing PRP with placebo and with alternatives other than hyaluronic acid are needed to determine the efficacy of PRP for knee and hip OA. Studies are also needed to determine the optimal protocol for delivering PRP. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Adjunct to Surgery**
For individuals with anterior cruciate ligament reconstruction who receive PRP injections plus orthopedic surgery, the evidence includes 2 systematic reviews of multiple RCTs and prospective studies. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Only 1 of the 2 systematic reviews conducted a meta-analysis; it showed that adjunctive PRP treatment did not result in a significant effect on International Knee Documentation Committee scores, a patient-reported, knee-specific outcome measure that assesses pain and functional activity. Individual trials have shown mixed results. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with hip fracture who receive PRP injections plus orthopedic surgery, the evidence includes an open-labeled RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The single open-labeled RCT failed to show a statistically significant reduction in the need for surgical revision with the addition of PRP treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with long bone nonunion who receive PRP injections plus orthopedic surgery, the evidence includes 3 RCTs. Relevant outcomes are symptoms, functional outcomes, health
status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. One trial with a substantial risk of bias failed to show significant differences in patient-reported or clinician-assessed functional outcome scores between those who received PRP plus allogenic bone graft and those who received only allogenic bone graft. While the trial showed a statistically significant increase in the proportion of bones that healed in patients receiving PRP in a modified intention-to-treat analysis, the results did not differ in the intention-to-treat analysis. The second RCT, which compared PRP with recombinant human bone morphogenetic protein-7, also failed to show any clinical or radiologic benefits of PRP over morphogenetic protein. The third RCT reported no difference in the number of unions or time to union in patients receiving PRP injections versus no treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with rotator cuff repair who receive PRP injections plus orthopedic surgery, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Although systematic reviews consistently found significant reductions in pain with platelet-rich plasma at 12 months, important study conduct and relevance weaknesses limit interpretation of these findings. Additionally, the pain reductions with platelet-rich plasma were not maintained in longer-term studies. Further, the systematic reviews and meta-analyses failed to show a statistically and/or clinically significant impact on other outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals undergoing spinal fusion who receive platelet-rich plasma injections, the evidence includes a single small RCT and two observational studies. Relevant outcomes include symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Studies have generally failed to show a statistically and/or clinically significant impact on symptoms (ie, pain). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with subacromial decompression surgery who receive PRP injections plus orthopedic surgery, the evidence includes a small RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. A single small RCT failed to show a reduction in self-assessed or physician-assessed spinal instability scores with PRP injections. However, subjective pain, use of pain medications, and objective measures of range of motion showed clinically significant improvements with PRP. Larger trials are required to confirm these benefits. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with total knee arthroplasty who receive PRP injections plus orthopedic surgery, the evidence includes a small RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The RCT showed no significant differences between the PRP and untreated control groups in bleeding, range of motion, swelling around the knee joint, muscle power recovery, pain, or Knee Society Score and Knee Injury and Osteoarthritis Outcome Score. The evidence is insufficient to determine the effects of the technology on health outcomes.
SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Academy of Orthopaedic Surgeons
In 2013, the American Academy of Orthpaedic Surgeons (AAOS) guidelines did not recommend for or against growth factor injections and/or platelet-rich plasma (PRP) for patients with symptomatic osteoarthritis of the knee.(57) A recommendation of inconclusive was based on a single low-quality study and conflicting findings that did not permit a recommendation for or against the intervention. The AAOS recommendation was based on 3 studies published before May 2012.

In 2017, the AAOS issued evidence-based guidelines on the management of OA of the hip.(58) In the section on intra-articular injectables, the guidelines stated that there is strong evidence supporting the use of intra-articular corticosteroids to improve function and reduce pain in the short term for patients with osteoarthritis of the hip. There was also strong evidence that the use of intra-articular hyaluronic acid does not perform better than placebo in improving function, stiffness, and pain in patients with hip osteoarthritis. The guidelines also noted that there were no high-quality studies comparing platelet-rich plasma with placebo for the treatment of osteoarthritis of the hip.

National Institute for Health and Clinical Excellence
In 2013, the National Institute for Health and Care Excellence (NICE) issued guidance on use of autologous blood injection for tendinopathy.(59) The NICE concluded that the current evidence on the safety and efficacy of autologous blood injection for tendinopathy was “inadequate” in quantity and quality.

In 2013, the NICE also issued guidance on use of autologous blood injection (with or without techniques for producing platelet-rich plasma) for plantar fasciitis.(60) The NICE concluded that the evidence on autologous blood injection for plantar fasciitis raised no major safety concerns but that the evidence on efficacy was “inadequate in quantity and quality.”

In 2019, the NICE issued guidance on use of platelet-rich plasma for osteoarthritis of the knee.(61) The NICE concluded that current evidence on platelet-rich plasma injections for osteoarthritis of the knee raised “no major safety concerns”; however, the “evidence on efficacy is limited in quality.” Therefore, the NICE recommended that “this procedure should only be used with special arrangements form clinical governance, consent, and audit or research.”

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 19.
Table 19. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>Ongoing</td>
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<tr>
<td>NCT01843504</td>
<td>Platelet-Rich Plasma (PRP) Injection for the Treatment of Chronic Patellar Tendinopathy</td>
<td>44</td>
<td>December 2023</td>
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<tr>
<td>NCT03138317</td>
<td>Evaluation of Platelet Rich Plasma (PRP) for Knee Osteoarthritis</td>
<td>60</td>
<td>May 2018</td>
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<tr>
<td>NCT01668953</td>
<td>Impact of Platelet Rich Plasma Over Alternative Therapies in Patients With Lateral Epicondylitis (IMPROVE)</td>
<td>100</td>
<td>March 2020</td>
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<tr>
<td>NCT03129971</td>
<td>Platelet-Rich Plasma Combined with Conventional Surgery in the Treatment of Atrophic Nonunion of Femoral Shaft Fractures</td>
<td>92</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT01833598</td>
<td>Percutaneous Needle Tenotomy (PNT) Versus Platelet Rich Plasma (PRP) with PNT in the Treatment of Chronic Tendinosis</td>
<td>40</td>
<td>Oct 2022</td>
</tr>
<tr>
<td>NCT02984228</td>
<td>Platelet-rich Plasma vs. Hyaluronic Acid for Glenohumeral Osteoarthritis</td>
<td>70</td>
<td>Nov 2020</td>
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<tr>
<td>NCT02923700</td>
<td>Leukocyte-rich platelet-rich plasma (PRP) vs Leukocyte-poor platelet-rich plasma (PRP) for the Treatment of Knee Cartilage Degeneration: a Randomized Controlled Trial</td>
<td>192</td>
<td>Dec 2020</td>
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<tr>
<td>NCT02872753</td>
<td>Intra-operative platelet-rich plasma (PRP) Injection Following Partial Meniscectomy</td>
<td>90</td>
<td>Mar 2021</td>
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<tr>
<td>NCT03300531</td>
<td>Autologous Pure Platelet-rich Plasma in the Treatment of Tendon Disease: A Randomized Controlled Trial</td>
<td>540</td>
<td>Dec 2021</td>
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<tr>
<td>NCT04241354</td>
<td>A Comparison of Platelet-rich Plasma Treatment to the Intra-articular vs. Intra- and Extra-articular Environments in Patients Diagnosed With Hip Osteoarthritis</td>
<td>84</td>
<td>Dec 2021</td>
</tr>
<tr>
<td>NCT03136965</td>
<td>Platelet-Rich Plasma Therapy for Patellar Tendinopathy platelet-rich plasma (PRP)</td>
<td>66</td>
<td>Aug 2022</td>
</tr>
<tr>
<td>NCT03984955</td>
<td>A Prospective, Double Blind, Single Centre, RCT, Comparing the Effectiveness of Physiotherapy in Addition to One of 3 Types of Image Guided Injection of the Common Extensor Tendon, on Pain and Function in Patients With Tennis Elbow</td>
<td>123</td>
<td>April 2023</td>
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<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT01915979</td>
<td>Role of Biological Therapy in Rotator Cuff Tendinopathy. Effectiveness of Plasma Rich in Growth Factors Regarding Functional Capacity and Pain Compared With the Conventional Treatment Using Steroids</td>
<td>84</td>
<td>Dec 2016(completed)</td>
</tr>
<tr>
<td>NCT02694146</td>
<td>Clinical Trial to Evaluate the Use of Platelet Rich Plasma in Front Hyaluronic Acid in Coxarthrosis</td>
<td>74</td>
<td>May 2018</td>
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<tr>
<td>NCT03133416</td>
<td>Platelet-Rich Plasma Injections and Physiotherapy in the Treatment of Chronic Rotator Cuff Tendinopathy</td>
<td>165</td>
<td>July 2018</td>
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<tr>
<td>NCT01406821</td>
<td>Treatment of Acute and Chronic Ligament and Tendon Injuries with Platelet Rich Plasma</td>
<td>30</td>
<td>March 2019</td>
</tr>
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</table>

NCT: national clinical trial
* Denotes industry-sponsored or cosponsored trial.
Government Regulations
National:
There is no national coverage determination (NCD) on this topic.

Local:
There is no local coverage determination (LCD) on this topic.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Orthopedic Applications of Stem Cell Therapy
- Prolotherapy
- Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Non-Orthopedic Conditions

References


The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 3/2/21, the date the research was completed.
### Joint BCBSM/BCN Medical Policy History

<table>
<thead>
<tr>
<th>Policy Effective Date</th>
<th>BCBSM Signature Date</th>
<th>BCN Signature Date</th>
<th>Comments</th>
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</thead>
</table>
| 5/1/16                | 2/16/16              | 2/16/16            | Routine maintenance  
Topic previously addressed on policy, “Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Miscellaneous Conditions.” |
| 5/1/17                | 2/21/17              | 2/21/17            | Routine maintenance |
| 11/1/17               | 8/15/17              | 8/15/17            | Routine maintenance |
| 11/1/18               | 8/21/18              | 8/21/18            | Routine maintenance |
| 11/1/19               | 8/20/19              |                    | Routine maintenance |
| 7/1/20                | 4/14/20              |                    | Code update, added C1734 |
| 7/1/21                | 4/20/21              |                    | Routine maintenance  
Ref 7,12,13,14,15,18,19,20,30,31,32,43,50,51,52 added |

Next Review Date: 2nd Qtr, 2022
# Blue Care Network Benefit Coverage Policy: Orthopedic Applications of Platelet-Rich Plasma

## I. Coverage Determination:

<table>
<thead>
<tr>
<th>Plan Type</th>
<th>Coverage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial HMO (includes Self-Funded groups unless otherwise specified)</td>
<td>Not covered</td>
</tr>
<tr>
<td>BCNA (Medicare Advantage)</td>
<td>See Government Regulations section.</td>
</tr>
<tr>
<td>BCN65 (Medicare Complementary)</td>
<td>Coinsurance covered if primary Medicare covers the service.</td>
</tr>
</tbody>
</table>

## II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.